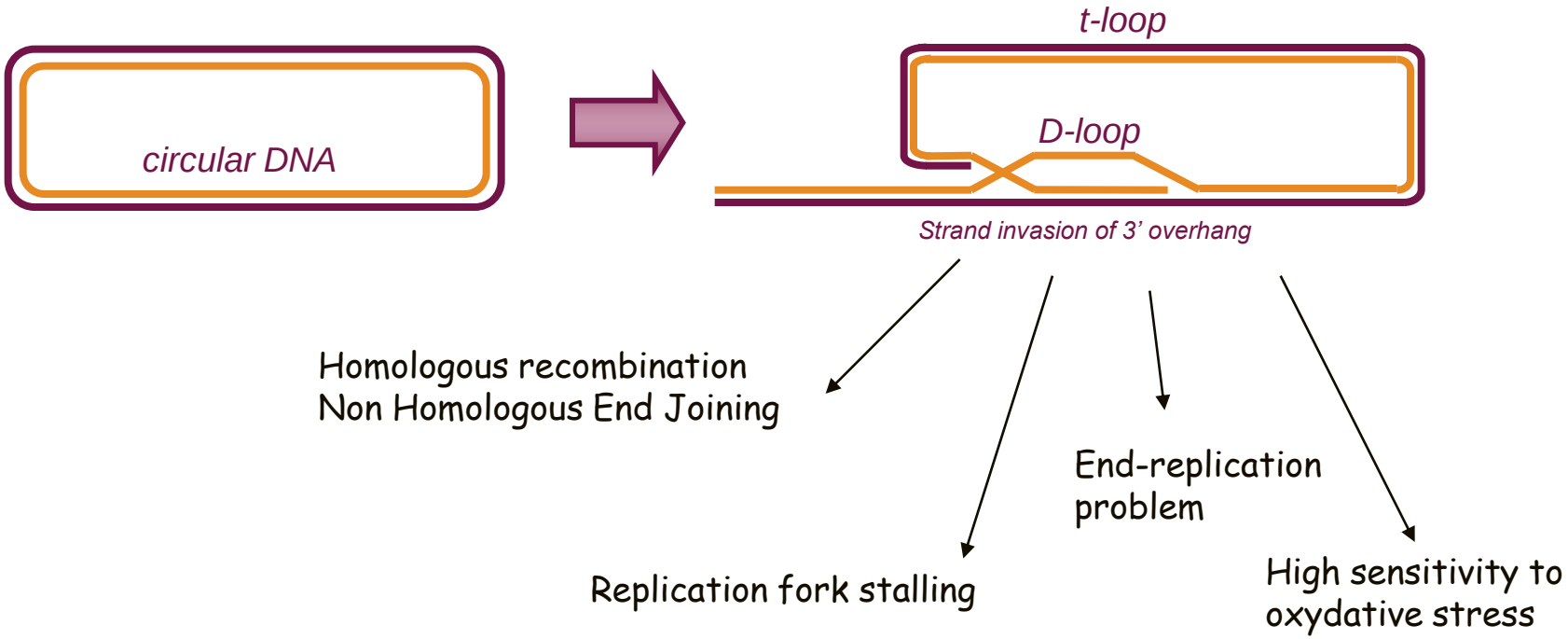
Short telomeres (ST) correlate with vulnerability, toxicity and early death in elderly AOC patients receiving carboplatin: a multicenter GINECO study trial.

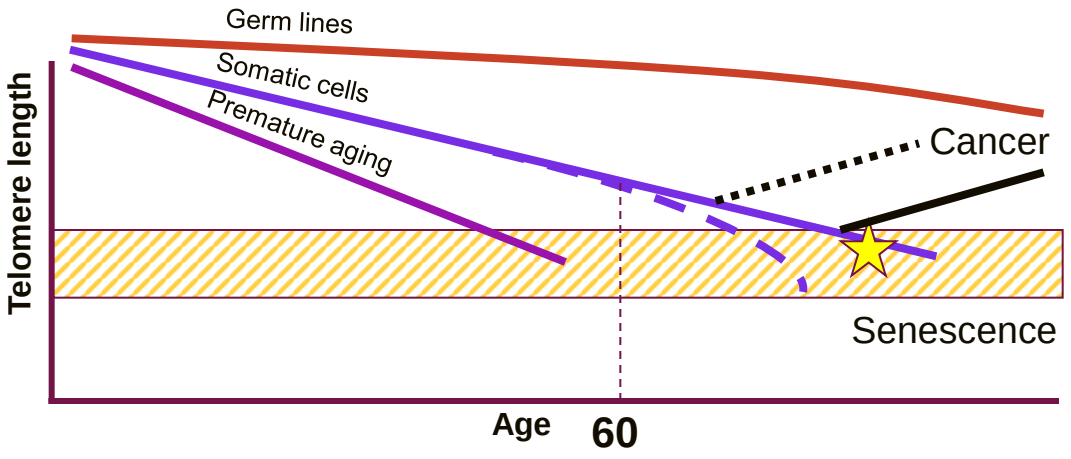
Falandry C., Horard B., Alexandre J., Deplanque D., Cojocarasu O., Salvat J., Legouffe E., Cretin J., Meunier J., Maraval-Gaget R., Micheau-Bonnier D., Gilson E., Freyer G.

The telomere connection



Hayflick L. Exp Cell Res 1961;25:585-621.
Olovnikov AM. J Theor Biol 1973;41:181-90.
Greider CW. Cell 1987;51:887-98.
Rudolph KL. Cell 1999;96:701-12.

Telomere and aging



Telomerase activation

ALT telomere lengthening

Chromosomal recombinations – telomere healing

Tissue renewal loss

Pro-inflammatory secretory phenotype

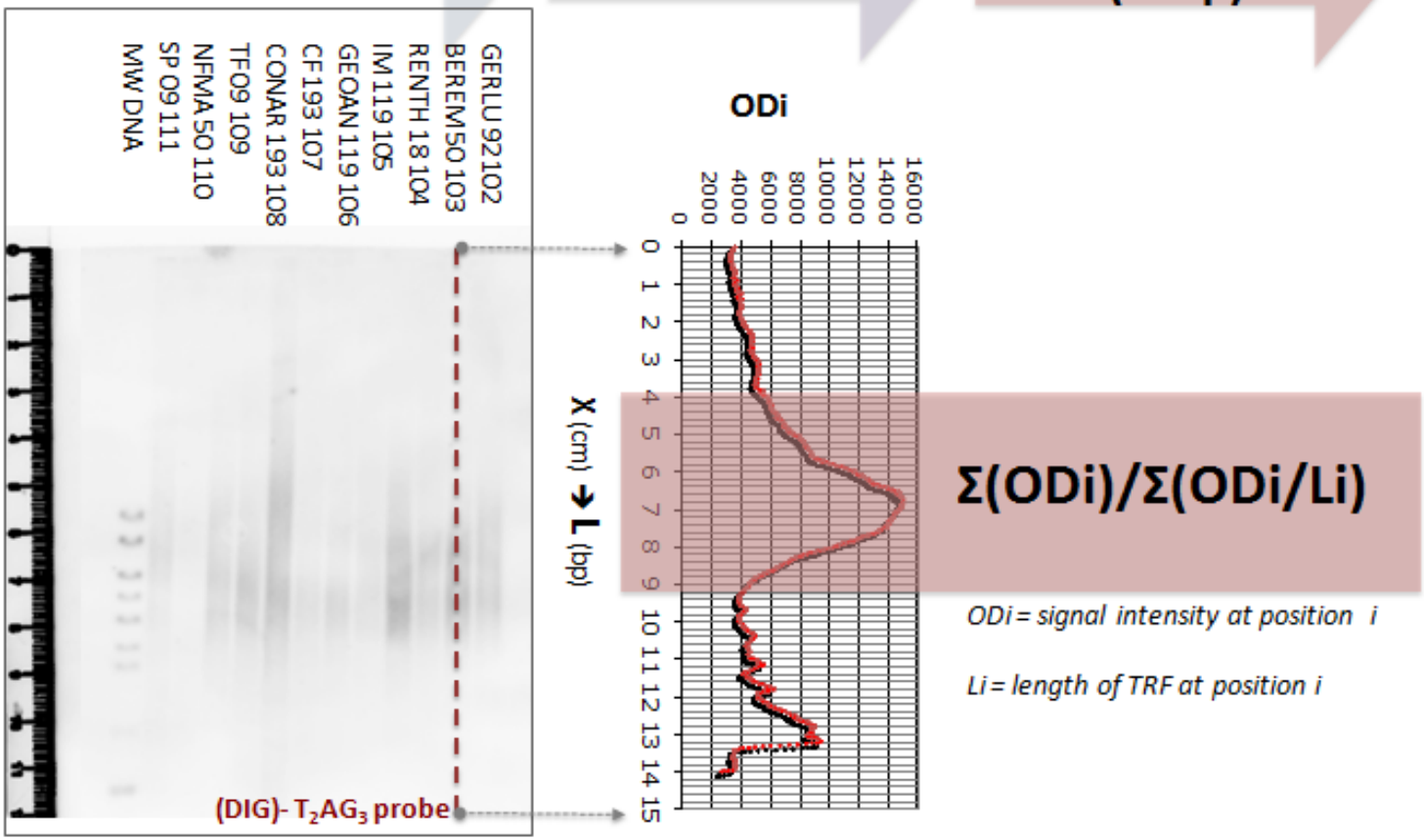
Pro-tumorogenic potential

- loss of telomerase activity ?
- Higher turn over ?
- Inflammaging ?
- Oxydative stress ?

Method

Peripheral blood leukocyte Telomere length

Southern Analysis of Terminal Restriction Fragments → **Image J treatment** → **Mean TRF Length (in bp) ***



$$\Sigma(ODi)/\Sigma(ODi/Li)$$

ODi = signal intensity at position i

Li = length of TRF at position i

** According to Harley et al. 1990, Nature 345*

Ovarian cancer in the elderly

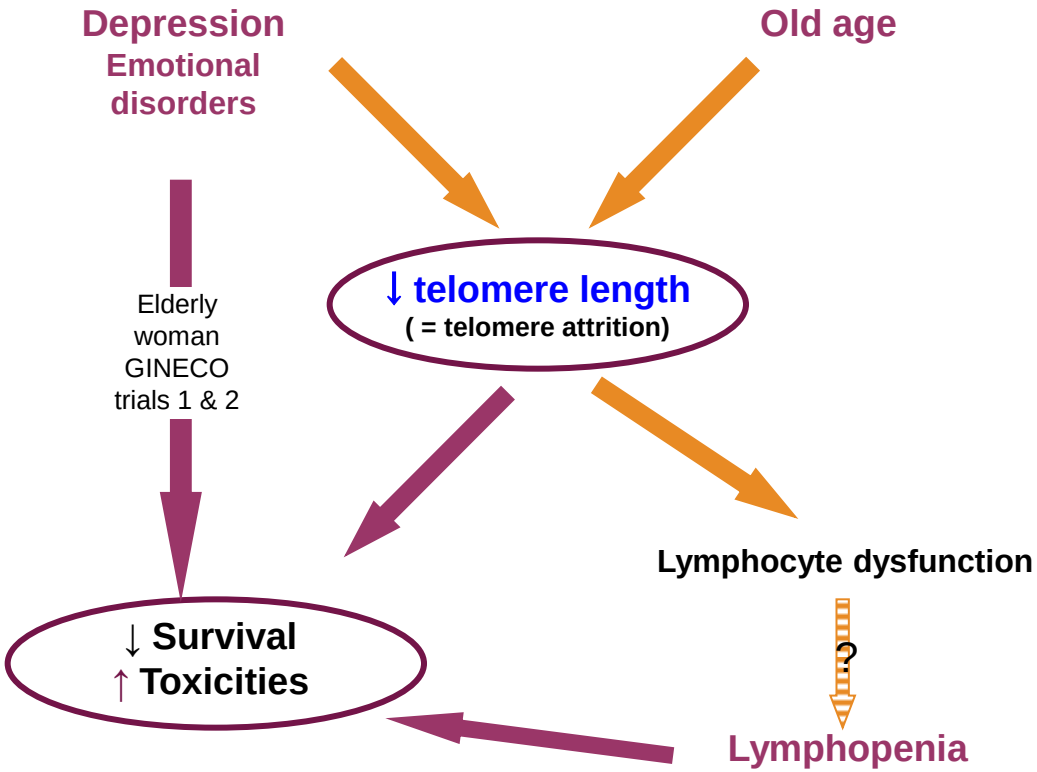
- Subgroup analyses: standards feasible in selected elderly patients : primary surgery, carboplatin-paclitaxel
- GINECO experience: treatment completion rate
  - ✓ 1999-2003: 72% for carboplatin-cyclophosphamide (n=83)
  - ✓ 2004-2006: 68% for carboplatin-paclitaxel (n=75)

Multivariate analysis: negative impact of

- Age
- Stage (IV vs III)
- Paclitaxel-based treatment
- **Depression and emotional disorders**
- **Lymphopenia**

Freyer G. Ann Oncol 2005;16:1795-800.
Trédan O. Ann Oncol 2007;18:256-62

The telomeric working hypothesis



Cawthon RM. Lancet 2003;361:393-5.
Epel ES. Proc Natl Acad Sci U S A 2004;101:17312-5.

Elderly woman GINECO trial 3

- 111 patients with stage III/IV ovarian cancer
  included from 08/2007 to 01/2010
  treated with 6 cycles of carboplatin monotherapy (AUC5),
  +/- primary cytoreduction

- Primary endpoint: Impact of geriatric covariates on survival

- Secondary endpoint:
  - **Impact of telomere length** on treatment completion rate (TCr), tolerance and overall survival.
    Standard Terminal Restriction Fragment analysis performed at inclusion, after 3 and 6 cycles

Patients characteristics

Total (%)	111 (100)
Age (years)	
Median	78
≥ 80	45 (41)
Extremes	70-93
Performance status	
0-1	63 (57)
2-3	48 (43)
≥ 1 dependence ADL	61 (55)
≥ 1 dependence on IADL	93 (75)
Emotional disorders	
Screening	20 (18)
HADS ≥ 15	41 (37)
≥ 4 co-medications	76 (69)

Development of a Geriatric Vulnerability Score (GVS) in multivariate analysis

GVS = $\sum$ **vulnerability factors :**

Major :
- score ADL < 6
- score IADL < 25
- albuminemia < 35g/L

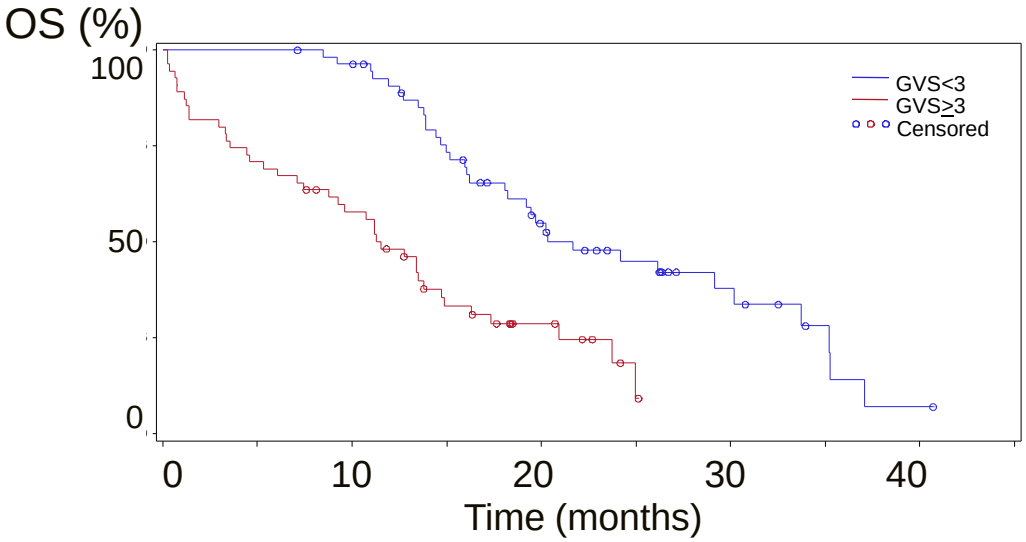
Minor :
- Lymphopenia < 1G/L
- score HADS > 14

=> Vulnerable if **GVS ≥ 3**

See poster 9079 by Freyer, G. et al.:

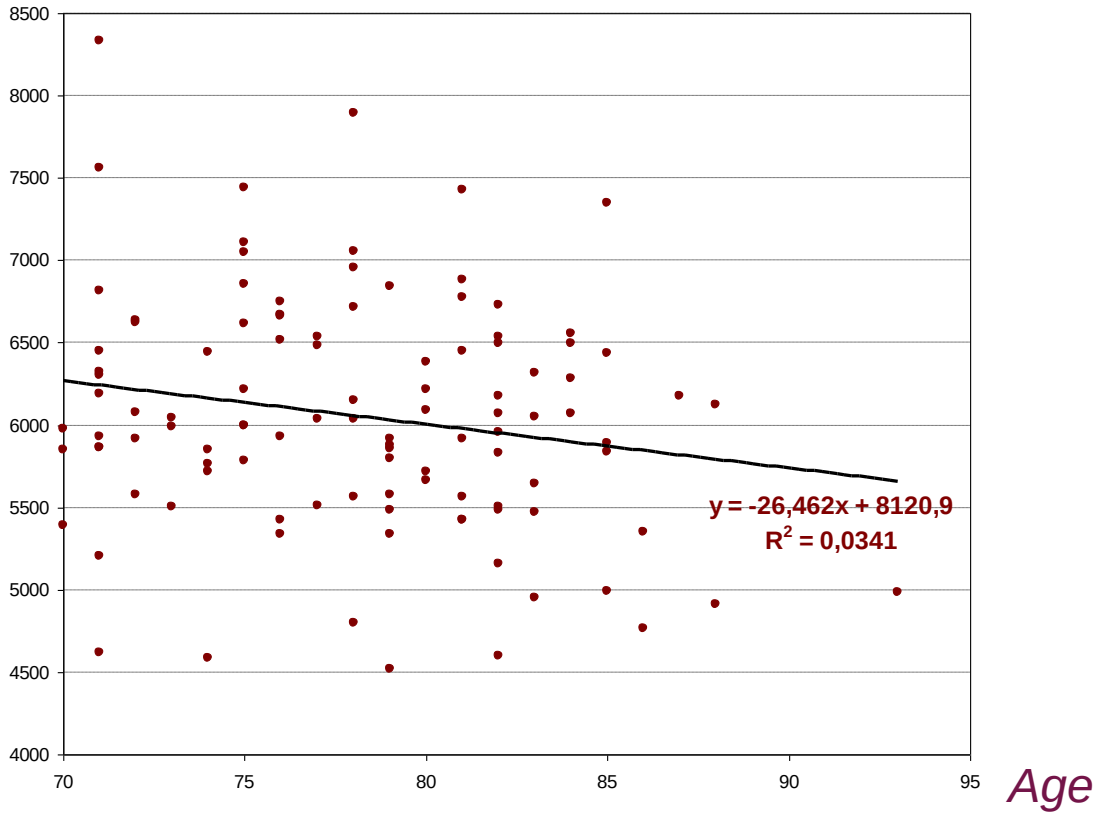
Patient and survivor care

Sat June 2: 8:00-12:00



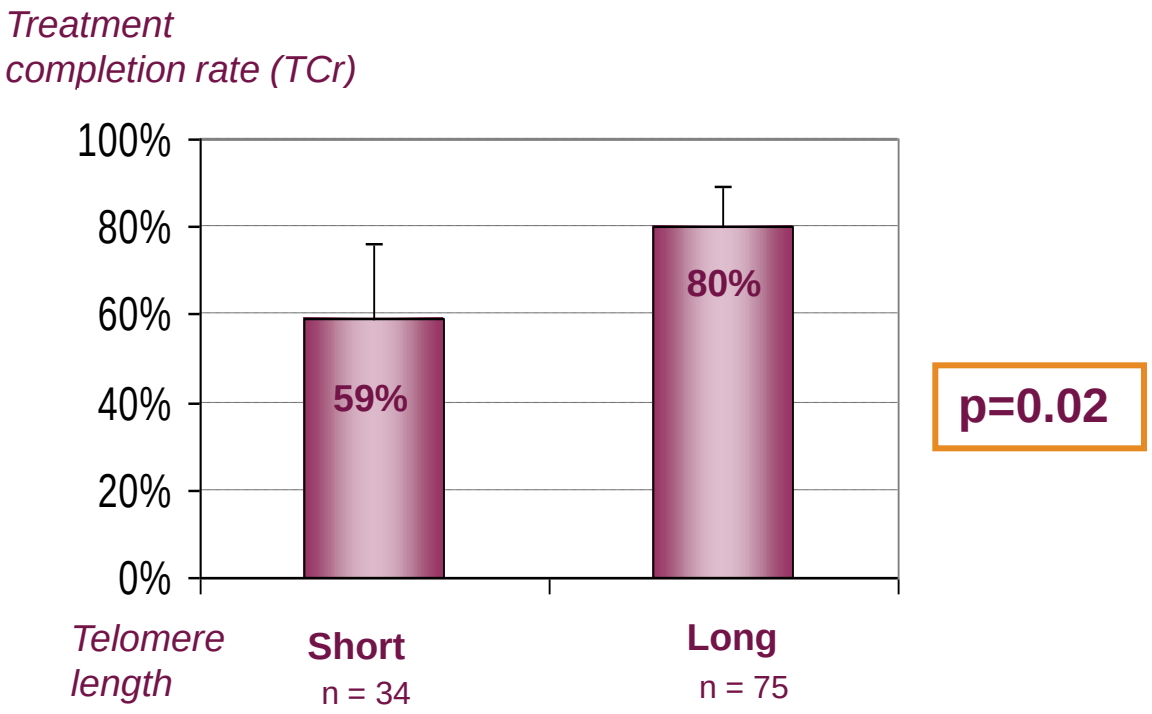
A weak correlation between telomere length and age

- 111 patients sampled, 109/111 evaluable (duplicate analysis)



Patient telomere length and treatment completion rate (TCr)

- With a cut-off of 5770bp, TL discriminates 2 groups of patients with different TCr



Severe toxicity increases with telomere shortening

event	Observed Risk: short/long telomere group	95% confidence interval	P
Serious Adverse Events	**2.69**	**1.17-6.19**	**.019**
Unplanned hospital admissions	2.14	0.92-4.95	.070
Grade ≥ 3 non-hematological toxicities	2.04	0.88-4.71	.095

Vulnerability increases with telomere shortening

- No significant correlation with any of the GVS components
- BUT a correlation between patient telomere length (Short vs Long) and vulnerability (GVS ≥ 3; ≥ 2 major criteria)

GVS = $\sum$ vulnerability factors :

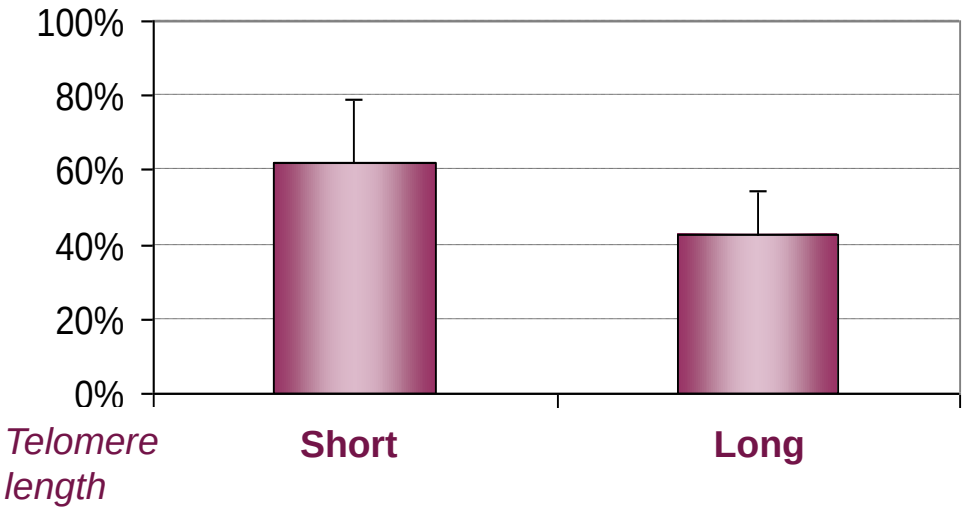
Major : - score ADL < 6
- score IADL < 25
- albuminemia < 35g/L

Minor : - Lymphopenia < 1G/L
- score HADS > 14

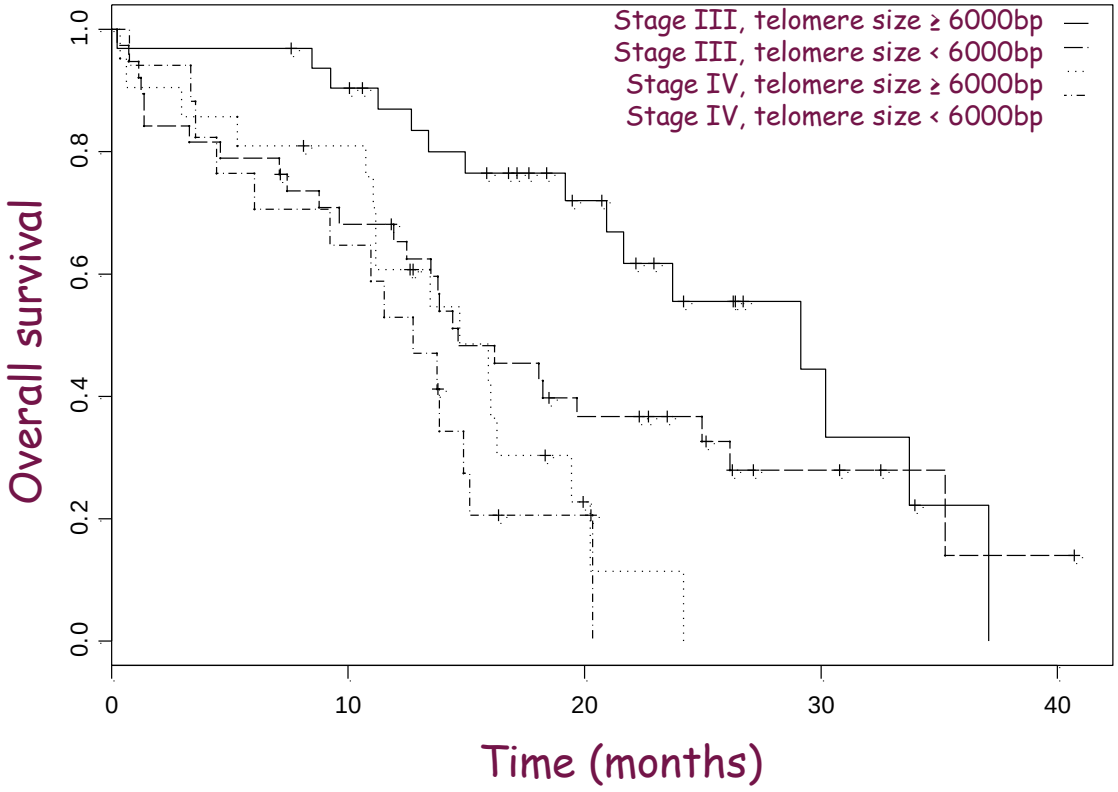
=> Vulnerable if **GVS ≥ 3**

Vulnerable pts (GVS ≥ 3; ≥ 2 major C, %)

OR = 2.17, p=0.06



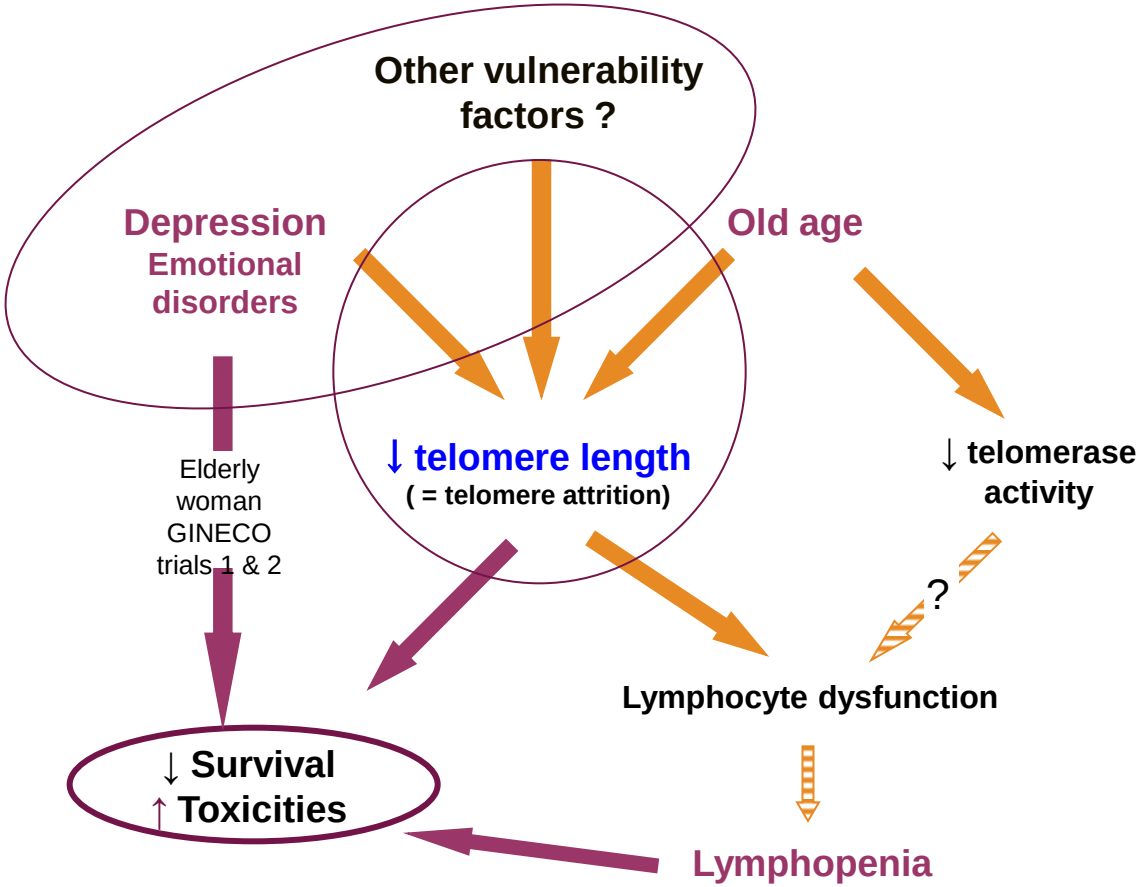
Overall survival



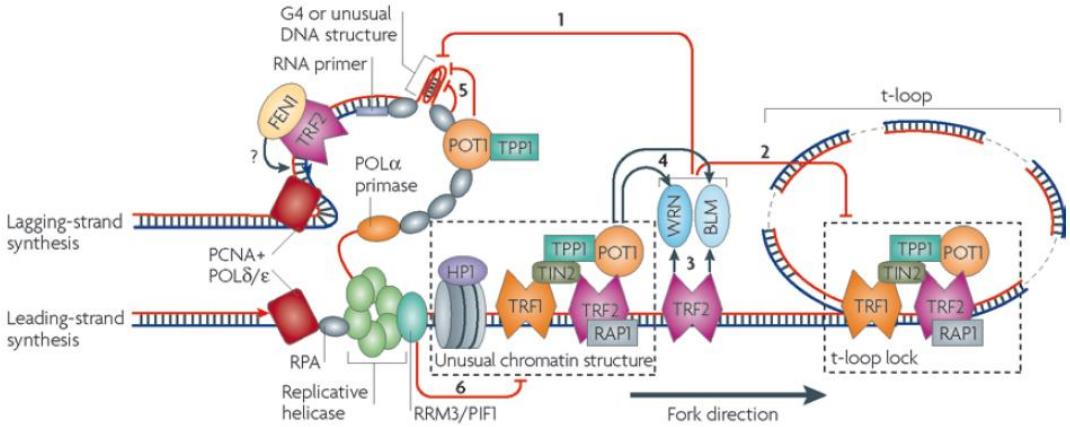
- Multivariate analysis :
  - Stage (IV vs III) HR=2,53 [1.54-4.27]; p=0,0003
  - Telomere < 6000bp HR=1,57 [0.98-2.51]; p=0,06

Back to the telomeric working hypothesis

- A partial overlap between TL and geriatric vulnerability factors



Dealing with controversies



From Gilson and Geli, Nat Rev Mol Cell Biol 2007

- Measuring directly DNA damage response
  - In cell nuclei : TIFs (Telomere-dysfunction Induced Foci)
  - DNA-damage biomarkers

Jiang et al, Proc Natl Acad Sci U S A 2008;105:11299-304.
Augereau et al, Blood 2011;118:1316-22.

Take home messages

Telomere length estimation

- is feasible using standard procedure
- Identifies a group of elderly patients with Short Telomeres who:
  - Have a lower chance to complete their planned 6 chemotherapy courses
  - Have a higher risk of chemotherapy toxicity (number of serious adverse events, unplanned hospital admissions and severe non-haematological grade 3-4 toxicity)
  - Partially overlaps with patient subsets according to the vulnerability score GVS
  - Might be a risk factor for premature death independent from FIGO stage

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